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(54) [Title of the Invention] Dermatologic Topical Composition

(57) [Abstract]

[Topic] To provide a dermatologic topical composition of a superior beautifying action on the skin and of superior safety and stability.

[Means of Solution] A dermatologic topical composition characterized in that it contains (A) a substance that inhibits or controls tyrosinase activity, (B) an extract selected from soybean cakes or fermented substances of which they are the raw materials and/or (C) flavonoid extracts of licorice or substances containing its components.

Claims]

[Claim 1] A dermatologic topical composition characterized in that it contains (A) a substance that inhibits or controls tyrosinase activity, (B) an extract selected from soybean cakes or fermented substances of which they are the raw materials and/or (C) flavonoid extracts of licorice or substances containing its components.

[Detailed Description of the Invention]

[0001]

[Technological field of the invention]  
This invention relates to a dermatologic topical composition that has superior skin beautifying action.

[0002]

[Prior art] There are many points concerning the mechanism of occurrence of pigment deposition in the skin such as liver spots and freckles. However, hormonal abnormalities and stimulation by ultraviolet rays are generally the causative factors and it is thought that the pigment melanin, which is produced in excess, is the abnormal deposit in the skin. With the objective of preventing or improving pigment deposition, attempts have been made to use beautifying cosmetic materials containing peroxides such as hydrogen peroxide, zinc peroxide and magnesium peroxide or ascorbic acid, glutathione, colloidal sulfur and various natural substances as the effective

constituents. However, many of these effective constituents are not of sufficient safety or stability or there is a problem of odor. Even if there is an effect, it is not necessarily sufficient. In the United States, hydroquinone is used as a skin decolorant. However, hydroquinone has irritating and allergic effects and, from the standpoint of safety, there are problems in compounding it as an effective component in cosmetics. Consequently, various studies have been conducted for the purpose of developing a cosmetic material that exhibits a skin beautifying effect without such drawbacks.

[0003] It is thought that excessive production of the pigment melanin is a major cause of pigment deposition in the skin such as liver spots and freckles. The most important enzyme that is operative in the production of the pigment melanin is tyrosinase. Tyrosinase is an enzyme that oxidizes tyrosine, which is the raw material of the pigment melanin. Research has been conducted on inhibiting or controlling the action of this enzyme for the purpose of inhibiting production of the pigment melanin. As the result, natural drug extracts of mulberry husk, senkyu [Cnidium], Angelica, cassia bark and Prunella (Fragrance Journal, June 1990, p. 59), topical beautifying agents in which kojic acid and kojic acid derivatives are used (Japanese Patent Application Early Disclosure No. Sho 53-3538 [1978], Japanese Patent No. Sho 56-18569 [1981], Japanese Patent Sho 58-22151 [1983], Japanese Patent Sho 60-9722 [1985] and Japanese Patent Sho 61-60801 [1986]), cosmetic materials in which quercetin is the effective constituent (Japanese Patent Application Early Disclosure No. Sho 55-92305 [1980]), cosmetic materials in which fatty acid esters of quercetin are the effective constituents (Japanese Patent Application Early Disclosure No. Sho 58-131911 [1983]), and cosmetic materials in which catechins having polyphenol skeletons are the effective constituents (Japanese Patent Application Early Disclosure No. Sho 52-44375 [1977]) are indicated. However, the stability of the beautifying constituents in these cosmetic materials is not sufficient on actual use, or, although an effect is found at the cellular level, there is the problem that the effect is not sufficiently manifested in human subjects so that they are not necessarily satisfactory.

[0004] In addition, extracts of licorice flavonoids, which are so-called oil-soluble licorice extracts, are substances in which glabridin is the principal component and it has been reported that they inhibit melanin production (Nihon Hifu Kagakkaishi [Journal of the Japanese Dermatological Chemistry Society], 102 (6) 679 (1992)). However, there are limitations on their beautifying effect and it has been indicated that they irritate the skin.

[0005] Accordingly, the inventors conducted an intensive search for substances that inhibit or control the activity of tyrosinase, which has the most important role in production of melanin, with the objective of providing a topical dermatologic agent with which the drawbacks of conventional topical dermatologic agents for beautification could be overcome, which would have a superior skin beautifying effect, which would be of high safety and stability and which would not present a problem of odor. As the result, they discovered that substances having a polyphenol skeleton, and, among them, ellagic acid compounds and alkali metal salts thereof were superior and they first proposed them (Patent Registration No. 1839986). The inventors then conducted further studies, and, as the result, found that effects even of these superior ellagic acid compounds and alkali metal salts thereof were not necessarily effective at the ordinary compounding concentrations for topical agents when they were compounded with the base compositions of cosmetic products and topical medicinal drug products.

[0006]

[Problems the invention is intended to solve] This invention has the objective of providing a topical dermatologic composition of a superior skin beautifying action and of superior safety and stability.

[0007]

[Means for solving the problems] In the light of the above-described circumstances, the inventors conducted repeated studies for the purpose of improving the skin beautifying effects of substances that inhibit or control tyrosinase activity, and of them, those that have a polyphenol skeleton and, in particular, of

preparations in which the above-described ellagic acid compounds and alkali metal salts thereof are compounded. As the result, they arrived at this invention by discovering that the beautifying effect is markedly increased without irritation of the skin when these substances, soybeans and soybean cakes or fermented substances of which they are the raw materials and/or (C) flavonoid extracts of licorice or substances containing its components are used in combination.

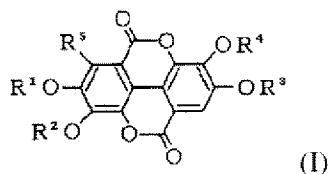
[0008] Specifically, this invention provides a dermatologic topical composition characterized in that it contains (A) a substance that inhibits or controls tyrosinase activity, (B) an extract selected from soybean cakes or fermented substances of which they are the raw materials and/or (C) flavonoid extracts of licorice or substances containing its components.

[0009]

[Embodiments of the invention] We shall now describe the various components of the dermatologic topical composition of this invention in specific terms. The substance that controls or inhibits the activity of tyrosinase, which is constituent A of the effective components of the dermatologic topical composition of this invention, is a single compound or a mixture, for example, an extract of a natural substance. These substances can be natural drug extracts of mulberry husk, senkyu [Cnidium], Angelica, cassia bark and Prunella (Fragrance Journal, June 1990, p. 59), and compounds such as ascorbic acid and kojic acid. In addition, the substances having a polyphenol skeleton can be catechins, tannin and lignin (Nihon Nogei Kagakkaishi [Journal of the Agricultural Chemical Society of Japan], 69 (9) 1183 1995). Further, they include ellagic acid compounds and alkali metal salts thereof. Of these, the effects of substances having polyphenol skeletons and, in particular, ellagic acid compounds and alkali metal salts thereof, are particularly good.

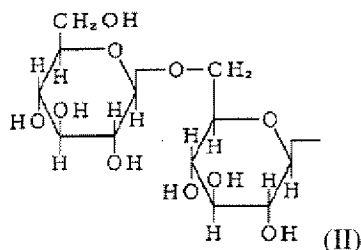
[0010] The above described ellagic acid compounds and alkali metal salts thereof are represented by the general formula indicated below.

[Chemical Formula 1]



(Wherein,  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are hydrogen atoms, alkyl groups of 1 to 20 carbon atoms, acyl groups of 1 to 20 carbon atoms, polyoxyalkylene groups of the general formula  $-(CmH_2m-O)nH$  (wherein  $m$  is an integer of 2 or 3 and  $n$  is an integer of 1 or greater), or a sugar residue indicated by the general formula

[Chemical Formula 2]



which substances may be the same or different from each other, and  $R^5$  indicates a hydrogen atom, an hydroxyl group or an alkoxy group of 1 to 8 carbon atoms.)

[0011] Specific examples of the case in which  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  in said general formula (I) are alkyl groups of 1 to 20 carbon atoms include methyl groups, ethyl groups and propyl groups, with methyl groups and ethyl groups being particularly desirable. Specific examples of the case in which  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  in said general formula (I) are acyl groups include acetyl groups and propionyl groups. In addition, Specific examples of the case in which  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  in said general formula (I) are  $-(CmH_2m-O)nH$  include polyoxyethylene groups and polyoxypropylene groups.  $n$  is an integer of 1 or greater, and, preferably of 5 to 40.  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  may be the same or different. Further, specific examples of the case in which  $R^5$  is an alkoxy group of 1 to 8 carbon atoms include methoxy groups, ethoxy groups and propoxy groups, with methoxy groups being particularly desirable. Moreover, the alkali metal salts of these ellagic acid compounds can be, for example, sodium salts or potassium salts.

#### [0012] Desirable ellagic acid

compounds of this invention can be, for example, ellagic acids in which  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  in said general formula (I) are all hydrogen atoms and substances in which  $R^1$ ,  $R^2$  and  $R^3$  are hydrogen atoms, methyl groups or ethyl groups and  $R^5$  is a hydrogen atom, a hydroxyl group or a methoxy group. In addition, substances in which some of the phenolic hydroxyl groups are sodium salts or potassium salts are particularly desirable from the standpoint of good solubility. In order to regulate the oleophilic or hydrophilic properties of the above-described ellagic acids and alkali metal salts thereof in topic dermatologic compositions, some of  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  in said general formula (I) may be substituted by any desired group selected from long-chain alkyl groups of up to 20 carbon atoms, long-chain acyl groups of up to 20 carbon atoms, polyoxyalkylene groups indicated by the general formula  $(CmH_2m-O)nH$  (provided that  $m$  is an integer of 2 or 3 and  $n$  is an integer of 1 or greater) and sugar residues represented by the above described structural formula (II) and  $R^5$  may be substituted by a long-chain alkoxy of up to 8 carbon atoms.

[0013] Specific examples of the above-described ellagic acid compounds or alkali metal salts thereof include ellagic acid (in general formula (I),  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ : hydrogen atoms), 3,4-di-o-methyl ellagic acid (in general formula (I),  $R^1$ : methyl group;  $R^2$ : methyl group;  $R^3$ : hydrogen atom;  $R^4$ : hydrogen atom;  $R^5$ : hydrogen atom), 3,3'-di-o-methyl ellagic acid (in general formula (I),  $R^1$ : hydrogen atom;  $R^2$ : methyl group;  $R^3$ : hydrogen atom;  $R^4$ : methyl group;  $R^5$ : hydrogen atom), 3,3',4-tri-o-methyl ellagic acid (in general formula (I),  $R^1$ : methyl group;  $R^2$ : methyl group;  $R^3$ : hydrogen atom;  $R^4$ : methyl group;  $R^5$ : hydrogen atom), 3,3',4,4'-tetra-o-methyl-5-methoxyellagic acid (in general formula (I),  $R^1$ : methyl group;  $R^2$ : methyl group;  $R^3$ : methyl group;  $R^4$ : methyl group;  $R^5$ : methoxy group), 3-o-ethyl-4-o-methyl-5-hydroxyellagic acid (in general formula (I),  $R^1$ : methyl group;  $R^2$ : ethyl group;  $R^3$ : hydrogen atom;  $R^4$ : hydrogen atom;  $R^5$ : hydroxyl group), Amritoside (in general formula (I),  $R^1$ : above described structural formula (II);  $R^2$ : hydrogen atom;  $R^3$ : hydrogen atom;  $R^4$ : hydrogen atom;  $R^5$ : hydrogen atom), and alkali metal salts of these compounds.

[0014] These ellagic acid compounds can easily be obtained by the method described below from such natural substances as strawberries, *Caesalpinia spinosa*, eucalyptus, apples, deutzia (*Coriaria japonica*), Radiata pine, bearberry, pomegranate, *Embilica officinalis*, *phyllidium*, *enfu* leaves, *gaiji* tea, *kakoku* leaves, oak, *kiju*, snake-weed roots and stalks, kounaka, sanukyu roots, sanukyuoyo, jufuboku, senkutssa, sogenro licorice, daihyouso, domoan leaves, haoben, bansekiryukan, bansekiryuhi, boka, gallnut, yatoseika, yukan roots, yukanbokuhi, yukan leaves, ryugasou roots, bansekiryu leaves, wakyobokukonbi, shido roots, chinjuso, and gennoshoko (See Japanese Patent Sho 53-14605 [1978]. [TRANSLATOR'S NOTE: Phonetic renderings are underlined.])\*

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\* [Translator's Note: Transliterated phonetically from the Japanese. As such, the spelling may differ from other transliterations.]

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[0015] Specifically, dried and pulverized products of the above-described natural substances containing ellagic acid compounds are steam-decomposed by the ordinary acidic sulfite method, after which they are immersed in alkaline aqueous solutions (pH 10 ~ 13) of sodium hydroxide and potassium carbonate. The immersing solution is removed, after which an acid such as sulfuric acid or acetic acid is added to the immersing solution to adjust the pH to 2 ~ 8, with a precipitate of which ellagic acid is the principal constituent being obtained. Ellagic acid of high purity can be obtained by collecting this precipitate by centrifugation and removing the insoluble matter by water washing. Ellagic acid compounds are present in a wide range of natural substances and are believed to be of extremely high safety. When, for caution's sake, safety was confirmed, no problems in practical use were found in terms of acute toxicity, skin irritability, skin sensitivity and mutagenicity, it being confirmed that they are of high safety.

[0016] In this invention, one or two or more of the compound that controls or inhibits tyrosinase activity, which is constituent A, mixtures thereof and natural extracts thereof can

be selected as desired. The compounding quantity should be 0.001 to 30% (% indicating wt%; the same hereafter), and, preferably, 0.05 to 10% of the entire topical dermatologic composition.

[0017] In the dermatologic topical composition of this invention, extracts can be selected from substances obtaining by fermenting soybean or soybean cake as the raw materials for constituent B in order to increase the beautifying effect of the above-described constituent A. The variety, cultivation site, cultivation and harvest time of the soybeans that serve as the raw material, and the external appearance, size and protein, fat and hydrocarbon content of the granules do not present any problems. (In regard to the soybeans, see Hiroyasu Fukuba, Ed., Selected Works of Eiyo University, "Soybeans," Publications Division, Joshi Eiyo University (1984).) In addition, there is no concern for pre-treatments after harvest such as drying, degreasing, deproteinization and pulverization. However, substances that have undergone steam boiling treatment and a fermentation process are desirable.

[0018] The term fermentation which is used here indicates action due to microorganisms or metabolic products thereof. That is, as required, microorganisms such as bacteria (*Bacilli*), yeast (*Saccharomyces*) and fungi (*Aspergillus*) are injected into soybeans or soybean cake that have been subjected to such pretreatments as immersion, steam boiling and pulverization and culturing is performed at a suitable temperature. At this time, there need not be any change in the culturing process regardless of whether one or several types of microorganism is used. In addition, even in direct culturing, microorganisms may also be added in such forms as *koji* [malt]. Consequently, there is no objection to adding organic substances such as rice and wheat, salts or water. The culture method may be solid or liquid and may be standing, stirred and shaken. Further, treatments may be performed using extracts or metabolic products of the microorganisms. Known products obtained by fermenting soybeans include *miso*, soy sauce, fermented soybeans [*natto*], *tenpe* [phonetic] and fermented beancurd. They may be used as raw materials.

[0019] Extraction may be performed by stir-shake, standing or circulation using water or organic solvents such as ethanol or mixtures thereof. Supercritical extraction with carbon dioxide can also be used. It is possible to obtain "constituent B" in unaltered form without extraction. However, there are great restrictions on effect, handling, external appearance and use feel in making topical dermatologic compositions.

[0020] It has been reported that extracts of *miso* have a melanin production inhibiting action in melanoma cells (Miso Science and Technology [Miso no Kagaku to Gijutsu], 43 (2) 68 (1995)) and that their effective constituent is in a non-dialyzable fraction (Journal of the Japanese Food Science Engineering Society [Nihon Shokuhin Kagaku Kogakkaishi] 43 (6) 712 (1996)). However, a beautifying effect was not found at which an effect could be expected at the actual use level.

[0021] The concentration of constituent B in this invention is the remainder when the extraction solvent has been removed. It should be 0.001 to 50%, and preferably 0.01 to 20%, and most preferably, 0.1 to 10%, of the topical dermatologic composition as a whole.

[0022] In addition, in the topical dermatologic composition of this invention, a flavonoid extract of licorice or a component thereof is used as constituent C for increasing the beautifying effect of the above-described constituent A. Said flavonoid extract of licorice is called an oil-soluble licorice extract. In this invention, an extract may be used as constituent C or a constituent such as glabridin may be contained in this extract.

[0023] In this invention, the concentration of constituent C should be less than 30%, preferably, 0.001 to 20%, and, more preferably, 0.01 to 10%, of the topical dermatologic composition as a whole.

[0024] Constituent A can be used in combination with constituent B and/or constituent C in the topical dermatologic composition as a whole. However, combined use of constituent A with constituent B and constituent C is desirable. The ratio of

concentrations of "constituent A" and "constituent B" and/or "constituent C" of the topical dermatologic composition of this invention should be 1 : 500000~5000 : 1, preferably, 1 : 4000~100 : 1, and, more preferably, 1 : 200~50 : 1.

[0025] As required, various constituents that are ordinarily used in topical dermatologic compositions can be compounded in addition to the above described "constituent A," "constituent B" and "constituent C" in the topical dermatologic composition of this invention in ranges that do not impair the effect of the invention, including, for example, humectants such as oils, water and surfactants, alcohol, thickeners, antioxidants, metal ion blocking agents, pH regulators, preservatives, fragrances, pigments, ultraviolet ray absorbents, ultraviolet ray scattering agents, vitamins and amino acids.

[0026] There is a broad range of base materials for the topical dermatologic composition of this invention, including aqueous solution systems, solubilization systems, emulsified systems, powder dispersion systems, water-oil two-layer systems, and water-oil-powder three-layer systems. They can be used in a broad range of forms including basic cosmetic materials such as creams, emulsions, toilet water, beautifying solutions and packs, makeup cosmetic materials such as lipstick and foundations, medicinal drug products such as jellies and ointments and non-medicinal drug products.

[0027]

[Working Examples] We shall now describe this invention in detail on the basis of working examples. First, various types of constituent B of the topical dermatologic composition of this invention as described below were prepared.

[Constituent B-1] Dried "Tsuru-no-ko [brand name] Soybeans" were thoroughly pulverized with a wooden mallet, after which 100 ml of ethanol was added and the mixture was stirred for 20 minutes at room temperature. It was filtered, after which the solvent was

removed under decreased pressure and 2.1 g of extract was obtained.

[Constituent B-2] 100 ml of 30% ethanol was added to 10 g of commercial *miso* and the mixture was stirred for 20 minutes at room temperature. After filtration, the solvent was removed under decreased pressure, after which it was dried in a desiccator and 1.5 g of extract was obtained.

[Constituent B-3] 100 ml of ethyl acetate was added to 100 ml of commercial Honjozo Soy Sauce and the mixture was thoroughly agitated with a separatory funnel. The mixture was allowed to stand, after which the solvent component, including the boundary component, was recovered. Extraction was again performed in the same way and the recovered solvent was removed under decreased pressure, after which it was dried in a desiccator and 0.4 g of extract was obtained.

[Constituent B-4] Defatted soybeans were steam boiled, after which they were pulverized, *Rhizopus arrhizus* was sown and fermentation was carried for 3 days at 40°C. 100 ml of 30% ethanol was added to 10 g of the former and the mixture was stirred thoroughly for 20 hours. After filtration, the solvent was removed under decreased pressure, after which it was dried in a desiccator and 1.4 g of extract was obtained.

[Constituent C] Substances described in the Classified Compounding Components Regulations for Cosmetic Products (Cosmetics

Compounding Regulations) were used as licorice flavonoid extracts.

#### [0028] Working Example 1

B16 melanoma cells were inoculated into a 6-well plastic microplate in amounts of  $2.5 \times 10^4$  cells/well and the cells were cultured for 2 days at 37°C in the presence of 5% CO<sub>2</sub>, after which the culture medium was replaced, constituent A and constituent B were added and the mixture was further cultured for 2 days. After culturing was concluded, the culture medium was discarded, the cells were stripped from the plate into a trypsin solution and transferred to an Eppendorf tube and the cells were then collected by centrifugation. They were washed with phosphoric acid buffered physiological saline solution, after which observations were made of changes in the color of the cells. The results are shown in Table 1. Evaluation of skin beautifying action was performed by comparing the changes in the color of the cells with the color of cells to which constituent A, constituent B and constituent C were not added on the following basis.

± : somewhat faded

+ : faded

++ : considerably faded

+++ : markedly faded.

[0029]  
[Table 1]

Constituent A	Constituent A/constituent C	Change in color of cells
Ellagic acid, 4 $\mu$ M	none	(+)
	B-1, 0.01%	++
	B-2, 0.01%	+++
	B-3, 0.01%	++
	B-4, 0.01%	+++
	C, 0.01%	++
	[B-1, 0.005% C, 0.005%	+++
Arbutin, 50 $\mu$ M	none	( $\pm$ )
	B-1, 0.01%	+
	B-2, 0.01%	++
	B-3, 0.01%	++
	B-4, 0.01%	++
	C, 0.01%	++
	[B-2, 0.005% C, 0.005%	+++
Kojic acid, 1 mM	none	(+)
	B-1, 0.01%	++
	B-2, 0.01%	+++
	B-3, 0.01%	++
	B-4, 0.01%	+++
	C, 0.01%	++
	[B-4, 0.005% C, 0.005%	+++

As should be evident from Table 1, when constituent B and/or constituent C were used in combination, more marked fading of the color of the B16 melanoma cells was found than when constituent A was used alone.

#### [0030] Working Example 2

Using ellagic acid as constituent (A), beautifying agent (1) consisting of constituent A dissolved in 1.0% propylene glycol, beautifying agent (2) consisting of the above-described constituent B-1 dissolved in 1.0% propylene glycol, beautifying agent (3) consisting of constituent A and constituent B-1 dissolved in 0.5% each of propylene glycol, beautifying agent (4) consisting of the constituent B-2 dissolved in 1.0% propylene glycol, beautifying agent (5) consisting of constituent A and constituent B-2 dissolved in 0.5% each of propylene glycol, beautifying agent (6) consisting of constituent B-4 dissolved in 1.0% of propylene glycol, and beautifying agent (7) consisting of constituent A and constituent B-4 dissolved in 0.5% each of propylene glycol,

were prepared and supplied to tests (7 animals in each group). Evaluation of skin beautifying action was performed by the method and evaluation standards indicated below. The results are shown in Table 3. The numbers in Table 3 show the Mancel values (average values for 7 animals) on application of the various test materials and control test materials.

[0031] [Beautification evaluation method] The fur on the backs of colored guinea pigs was shaved off with hair clippers and a shaver and pigment deposition of a range of approximately 2.25 cm<sup>2</sup> was made in two places on the back of each guinea pig by irradiation of ultraviolet rays once a day for a total of 8 times. Amounts of 20  $\mu$ l of the test materials and control test materials were applied once a day five times a week for 4 weeks and evaluations were made of changes in color value of pigment deposition once a week by visual observation using a standard color chart ("Neutral Value Scale 38" of the Japanese Color Institute (Inc.)). The differences in color values were calculated from the values converted to Mancel values as



described in the “Neutral Value Scale 38.” The term “difference in color value” indicates to what extent the change in the color value of the pigment deposition approaches the color skin in which there has been no pigment deposition due

to ultraviolet ray irradiation by comparison to the controls (to which only propylene glycol was applied). The evaluation was performed in accordance with the standards shown in Table 2.

[0032]

[Table 2]

Difference in color value	Less than 0.25	0.25 to 0.50	0.50 to 0.75	Greater than 0.75
Evaluation	ineffective ~ equal	somewhat effective	effective	markedly effective

[0033]

[Table 3]

Applied test material	Color value of test site	Color value of control site	Difference in color value	Pigment deposition evaluation
Beautifying agent 1 (A)	5.607	5.036	0.571	Effective
Beautifying agent 2 (B-1)	5.268	5.071	0.197	Ineffective
Beautifying agent 3 (A, B-1)	5.821	5.054	0.767	Markedly effective
Beautifying agent 4 (B-2)	5.321	5.071	0.350	Somewhat effective
Beautifying agent 5 (A, B-2)	5.911	5.089	0.822	Markedly effective
Beautifying agent 6 (B-4)	5.339	5.071	0.268	Somewhat effective
Beautifying agent 7 (A, B-4)	5.911	5.071	0.840	Markedly effective

As should be evident from Table 3, when soybeans, which constitute constituent B and, in particular, extracts obtained by fermenting soybeans, are used in combination, the beautifying effect is markedly greater than when ellagic acid, which comprises constituent A, is used alone.

[0034] Working Example 3

The oleaginous phase constituents and aqueous phase constituents shown in Table 4 were heated separately to 70°C and dissolved, after which they were mixed and emulsified. Fragrances were added as the substances were being cooled, after which they were cooled to room temperature, with emulsions being prepared.

[0035]

[Table 4]

Constituent	Working Example 3	Comparative Example 1	Comparative Example 2
Constituent A (ellagic acid)	0.5	1.0	-
Constituent B-2	0.5	-	1.0
Squalane	5.0	5.0	5.0
Isopropyl palmitate	2.0	2.0	2.0
Cetostearyl alcohol	1.2	1.2	1.2
Glycerol monostearate	1.3	1.3	1.3
Polyethylene glycol monostearate	1.5	1.5	1.5
Propylene glycol	5.0	5.0	5.0
Octyl glucoside	0.5	0.5	0.5
Carboxyvinyl polymer	0.1	0.1	0.1
Triisopropanolamine	0.1	0.1	0.1
Methylparaben	0.2	0.2	0.2
Purified water	balance	balance	balance
Fragrances	trace	trace	trace

[0036] The efficacy of the emulsions that were prepared in this way was evaluated as described below. That is, the product of this invention and comparative examples were applied twice a day for five weeks to pigment spots (liver spots) of ten men and women, after which the beautifying effect was studied after 5 weeks. The results are shown in Table 5. Evaluation of beautifying effect was performed in accordance with the following standard.

Markedly effective: Almost no pigment deposition was indicated.

Effective: Pigment deposition was extremely slight.

Somewhat effective: Pigment deposition was fairly slight.

Ineffective: No change  
S

[0037]

[Table 5]

Evaluation results	Markedly effective	Effective	Somewhat effective	Ineffective
Working Example 3	5	2	3	0
Comparative Example 1	0	3	5	2
Comparative Example 2	0	3	3	4

From the results in Table 5 it can be seen that the emulsion in which constituent A and constituent B of this invention were present together had a clearly superior beautifying effect as compared to the comparative examples in which they were used individually. No abnormalities in the state of the skin were observed during the five weeks in which the

above-described emulsions were used and after their use.

#### [0038] Working Example 4

The constituents shown in Table 6 were mixed and beautifying solutions were prepared.

[Table 6]

Constituent	Working Example 4	Comparative Example 1	Comparative Example 2
Sodium ellagate	0.75	0.75	-
Constituent B-3	0.75	-	0.75
Glycerol	4.0	4.0	4.0
Ethanol	8.0	8.0	8.0
Carboxyvinyl polymer	0.2	0.2	0.2
Triethanolamine	0.12	0.12	0.12
Purified water	balance	balance	balance

[0039] The efficacy of the beautifying solution which was a product of this invention that was prepared in this way was evaluated in the same

way as for Working Example 3 (except that the test period was 6 weeks). The results are shown in Table 7.

[Table 7]

Evaluation results	Markedly effective	Effective	Somewhat effective	Ineffective
Working Example 4	3	3	3	1
Comparative Example 3	0	4	4	2
Comparative Example 4	0	1	3	6

From the results in Table 7 it can be seen that the emulsion in which constituent A and constituent B of this invention were present together had a clearly superior beautifying effect as compared to the comparative examples in which they were used individually. No abnormalities in the state of the skin were observed during the six weeks in which the above-described emulsions were used and after their use.

[0040]

## Working Example 5

The oleaginous phase constituents and the aqueous phase constituents shown in Table 8

were dissolved separately at 70°C, after which the solutions were mixed while being stirred and emulsified. The substance was cooled to room temperature, with the cream shown in Table 8 being manufactured

[Table 8]

Constituent	Working Example 5	Comparative Example 5
Constituent A (ellagic acid)	0.5	1.0
Constituent B-4	0.5	-
Lanolin	2.0	2.0
Sorbitan monostearate	2.0	2.0
Polyoxyethylene sorbitan palmitate	2.0	2.0
Methyl glucoside mono-octyl ester	0.5	0.5
Beeswax	5.0	5.0
Squalane	10.0	10.0
Liquid paraffin	15.0	15.0
Propylene glycol	3.0	3.0
Dipropylene glycol	7.0	7.0
Methylparaben	0.2	0.2
Purified water	balance	balance

[0041] The efficacy of the cream agents that were prepared in this way were evaluated as described below. That is, amounts of 0.25 g of the creams were applied once a day each day for 6 weeks to the centers of pigment spots of 10

men and women (liver spots), after which the beautifying effect was studied. Evaluation of the beautifying effect was performed as in Working Example 3. The results are shown in Table 9.

[Table 9]

Evaluation results	Markedly effective	Effective	Somewhat effective	Ineffective
Working Example 5	2	4	3	1
Comparative Example 5	0	2	3	5

From the results in Table 9, it can be seen that the cream agents in which constituent A and constituent B, which was a product of this

invention, exhibited a clearly superior beautifying effect by comparison to the comparative example in which they were used

individually. No abnormalities in the state of the skin were observed during the six weeks in which the above-described cream agents were used and after their use.

[0042]

[Effect of the invention] Because the dermatologic topic composition of this invention was compounded using extracts obtained by

fermenting soybeans or soybean cakes as the raw material and/or licorice flavonoid extracts or constituents thereof as the substances that inhibit or control tyrosinase activity, their skin beautifying action was markedly higher than that of substances that inhibit or control tyrosinase activity used individually. Moreover, they were of superior safety for the skin, with no skin rashes occurring, and they were also of excellent stability.